REMARKS

Priority

The Examiner contends that the phrase "human gp39" in the instant claims does not find support in priority U.S. Patent Application No. 08/116,255 ("'255 application"), filed on September 2, 1993. For this reason, the Examiner opines that claims 82-94 are entitled only to the filing date of U.S. Patent Application No. 08/232,929, filed on April 24, 1994 (now U.S. Patent No. 5,869,049 (" '049 Patent")), from which the instant application also claims priority. The Examiner invites Applicants to provide support for the claims in the '255 application if Applicants desire priority to September 2, 1993[1]. Applicants respectfully traverse.

Support for the phrase "human gp39" of the pending claims is supported by the '049 Patent as well as the '255 application. Applicants direct the Examiner's attention, for example, to page 6, lines 10-19 and to page 8, lines 25-34 to page 9, lines 1-27 of the '255 application. In fact, this disclosure meets the written description and enablement requirements of 35 U.S.C. § 112, first paragraph. Applicants believe that the '255 application, as well as the '049 Patent, fully supports pending claims 82-94, including the phrase "human gp39". Accordingly, Applicants respectfully request that the pending claims 82-94 be accorded the filing date of the '255 application, September 2, 1993.

January 5, 2006 Office Action

Applicants acknowledge with appreciation the Examiner's withdrawal of the 35 U.S.C. § 112, first paragraph, lack of written description and lack of enablement rejections of claims 82-94. Applicants also acknowledge with appreciation the Examiner's withdrawal of the 35 U.S.C. § 112, second paragraph, indefiniteness.

[1] Applicants believe that in the June 14, 2006 Office Action, the Examiner inadvertently stated the priority date for the '255 application as "04/24/1994" instead of September 2, 1993, which is the filing date of the '255 application.

Applicants also acknowledge with appreciation the Examiner's withdrawal of the 35 U.S.C. § 103(a) obviousness rejections of claims 82-94 in view of U.S. Patent No. 6,264,951 and U.S. Patent No. 6,376,459.

Rejection Under 35 U.S.C. § 103(a)-Obviousness

The Examiner maintains his rejection of claims 82-94 as allegedly unpatentable over Lederman et al., U.S. Patent No. 6,403,091 ("Lederman"), in view of Beschorner et al., U.S. Patent No. 5,597,563 ("Beschorner"), Cobbold et al., U.S. Patent No. 5,690,933 ("Cobbold"), and Eynon et al., *J. Exp. Med.* 175: 131-138, 1992 ("Eynon"). The Examiner contends that these documents provide sufficient motivation to combine the teachings of the foregoing references to arrive at the claimed invention with a reasonable expectation of success, and that such a combination teaches each and every limitation of the claims. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the Examiner is over-generalizing the teachings of the cited art, and as a result, overlooks the details of the teachings. The Examiner's position is that Lederman provides for anti-gp39 antibodies that inhibit the immune response in order to treat various disease conditions, such as autoimmunity, and that the teachings of Beschorner, Cobbold, and Eynon makes it obvious to employ APCs to induce tolerance or a specific antigen to arrive at the claimed invention. However, there is no motivation whatsoever to combine Lederman with any of Beschorner, Cobbold, and Eynon.

Obviousness requires that each and every claim limitation be disclosed or suggested by the prior art. Lederman, Beschorner, Cobbold, and Eynon do not suggest the instant claims because they do not suggest all of the limitations of Applicants' claimed method for reducing antigen-specific T cell responsiveness. In their Amendment dated April 5, 2006, Applicants' amended claim 82 to recite a method for reducing antigen-specific T cell responsiveness comprising administration of (1) an antigen-presenting cell (APC) that presents an autoantigen to an activated

T cell expressing mouse or human gp39 **and** (2) an anti-gp39 antibody that binds to mouse or human gp39 on the activated T cell, wherein the anti-gp39 antibody is administered prior to, concurrent with, or subsequent to administration of the APC in an amount effective to reduce T cell responsiveness to the APC. Pending claim 82 recites a method that describes a specific manner for reducing antigen-specific T cell responsiveness that is not obvious over the cited prior art.

As previously acknowledged by the Examiner, Lederman fails to teach co-administration with APCs. The Examiner therefore attempts to cure Lederman's defect with Beschorner (which teaches induction of tolerance by depletion and re-population of thymic APCs), Cobbold (which teaches CD4 specific antibodies to support T cell immunity), and Eynon (which teaches that B cell presentation of antigen in the absence of help can elicit antigen-specific T cell anergy). The Examiner's attempts fail: there is no suggestion in the prior art to combine these references because there is no indication in these references as to the success of employing APCs to induce tolerance.

Both the motivation to combine the relevant elements and the suggestion of success must be found in the prior art to satisfy the requirements for maintaining an obviousness rejection. *In re The Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("[b]oth the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure"). While not all elements of the presently claimed method can be found in the cited references, finding various elements piecemeal in separate references is ***not*** sufficient motivation to combine them to arrive at a claimed invention. *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) ("[T]he examiner must show reasons that the skilled artisan, *confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.*") (citations omitted, emphasis added).

The references cited by the Examiner do not support a *prima facie* case of obviousness against claim 82, and claims 83-94 that depend therefrom, for a number of reasons.

The Examiner contends that "the teachings of Lederman et al. clearly provide for anti-CD40L (anti-5c8, anti-gp39, anti-CD40 ligand) antibodies to inhibit the immune response in order to treat disease conditions, such as autoimmunity." See Office Action, page 5. Applicants respectfully submit that the teachings of Lederman do not teach a person of skill in the art to treat an autoimmune disease because the model system used in Lederman is flawed. There are no data anywhere in Lederman showing the effect of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases. Indeed, there are no data showing the effect of normal human T cells expressing what is called T-BAM on an immune response *in vitro* or *in vivo*. Lederman does not teach anything about the treatment of autoimmune disease because it uses a human T cell line, Jurkat, which proliferates continuously in culture. One of skill in the art would not have used Jurkat T cells to study the role of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases because a Jurkat cell line is a transformed T cell leukemia line, and cannot be used to induce antigen-specific responses *in vitro* or *in vivo*.

Lederman used the Jurkat cell line as a convenient means to study B cell activation. This, however, is not the same as addressing the role of CD40-CD40L in autoimmune responses since antigen-specific responses were not examined. Furthermore, it was known that resting T cells do not express CD40L and that the expression of CD40L is regulated on T cells. Thus, using the Jurkat cell line, which is a continuously dividing T cell line, to activate B cells was not a good model for the interactions that could occur between normal T cells and B cells.

Moreover, Lederman does not provide evidence showing that monoclonal antibody 5c8 binds to cells other than human T cells and the Jurkat human T cell line, and certainly provides no evidence that monoclonal antibody 5c8 can affect an autoimmune disease in an animal including humans. There are no functional data in Lederman using activated T cells and no data assessing the role of anti-gp39 *in vivo* which would be essential to know if anti-gp39 could inhibit autoimmune disease. Thus, Lederman, as a primary reference, does not teach the use of an anti-gp39 antibody to treat autoimmune disease. Additionally, as stated above, it also does not disclose the co-administration of an anti-gp39 antibody with APCs.

Again the secondary references, do not cure Lederman's defects, and as shown below, are distinguishable from Applicants' invention.

(1) The Examiner in the current Office Action states that Beschorner discloses the use of APCs for inducing tolerance to autoantigens or self antigens in the treatment of autoimmune diseases by co-administration of APCs and an immunosuppressant and this disclosure, combined with Lederman, would render the present claims obvious. Applicants respectfully disagree. Actually, Beschorner teaches away from the present claims. Applicants remind the Examiner that it is an error to find obviousness where references "diverge from and teach away from the invention at hand." *W. L. Gore & Assoc. v. Garlock, Inc.*, 220 USPQ 303, 311 (Fed. Cir. 1983).

Beschorner discloses administration of APCs in an environment ***devoid*** of activated T cells, *i.e.*, subsequent to the use of a general immunosuppressive agent. On the other hand, Applicants' invention requires administration of APCs in an environment ***containing*** activated T cells. In fact, Applicants' claimed invention relies upon the existence of activated T cells expressing gp39. A skilled worker would not be motivated to combine the teachings of Beschorner with the teachings of Lederman because the skilled worker would recognize that an anti-gp39 antibody can only bind ***activated*** T cells, ***not unactivated*** T cells.

Furthermore, a skilled worker also would recognize that contact with an APC is necessary in order for T cells to become "activated" in the thymus and would understand that by administering an immunosuppressant, Beschorner teaches depletion of endogenous APCs in the thymus and thus, the depletion of mature, activated T cells, and any T cell pre-cursors.

(2) Cobbold fails to disclose any anti-gp39 antibodies much less co-administration of APCs with the antibodies. Cobbold merely discloses the co-administration of anti-CD4 and anti-CD8 monoclonal antibodies in order to induce T cell tolerance and prevent skin graft rejection (Cobbold, abstract, col. 3, ll. 15-16 and ll. 39-47).

In fact, the antibody taught by Lederman and the antibody taught by Cobbold each block T and B cell interaction with different mechanisms. Lederman's antibody blocks the "effector" phase (T cell induced differentiation of B cells into Ig-secreting cells), whereas Cobbold's antibody blocks the "inductive" phase (initial physical interaction of a T cell with a B cell), which is *prior* to the effector phase. Since Cobbold's method is already blocking the "inductive" phase, there would not be an "effector" phase to block following use of Cobbold's anti-CD4 antibody. Thus, one of ordinary skill in the art would not be motivated to look Cobbold's teachings in order to block the "effector" phase.

Additionally, neither Cobbold nor Lederman teaches co-administration of an antibody with an APC, which is a necessary claim limitation of Applicants' invention. Thus, a skilled worker would recognize that even improper combination of Cobbold with Lederman does not teach each and every aspect of Applicants' claimed method.

(3) Eynon fails to disclose administration of an APC. Rather, Eynon relies upon administration of an antigen only to induce transient tolerance by contacting small resting T cells and unprimed T cells for presentation to small resting B cells. The instant application may be further distinguished from Eynon. First, Applicants' invention requires co-administration of an APC and an anti-gp39 antibody; it does not rely upon endogenous APCs. Second, Eynon administers an endogenous APC to test whether T cell tolerance was induced. Thus, Eynon discloses a method of evaluating whether tolerance occurred, not for inducing tolerance.

Furthermore, a person of skill in the art would not be motivated to combine Eynon with Lederman with any reasonable expectation of success to arrive upon Applicants' claimed invention because the skilled worker would recognize that only activated, not resting, T cells express gp39 and Eynon only involves resting T cells.

Therefore, claim 82 is believed to be patentable over the cited art. In view of the patentability of claim 82, claims 83-94, which depend from this independent claim, are also

believed to be patentable. Applicants respectfully request reconsideration and withdrawal of this rejection.

In view of the above amendment, Applicants respectfully request that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

Dated: August 9, 2006

Respectfully submitted,

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